Oncology Practice Review™

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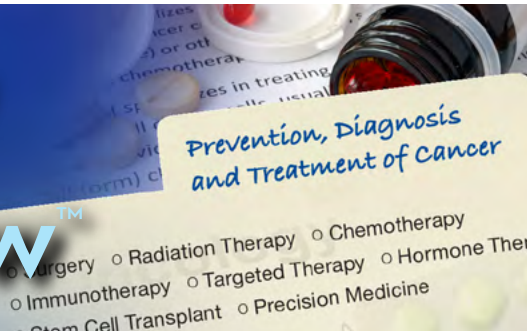
Issue 24 - 2023



In this issue:

Abbreviations used in this issue:

BAP1 = BRCA1-associated protein-1; **CEA** = carcinoembryonic antigen; **CTLA-4** = cytotoxic T-lymphocyte-associated protein 4; **DCBI** = dendritic cell-based immunotherapy; **ESMO** = European Society for Medical Oncology; **HIPEC** = heated intraperitoneal chemotherapy; **IHC** = immunohistochemistry; **NCCN** = US National Comprehensive Cancer Network; **OS** = overall survival; **PD-1** = programmed cell death protein 1; **PFS** = progression-free survival; **TTF-1** = thyroid transcription factor 1.

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Welcome to the 24th issue of Oncology Practice Review.

This Review covers news and issues relevant to clinical practice in oncology, with a focus on mesothelioma. It will bring you the latest updates, both locally and from around the globe, in relation to topics such as new and updated treatment guidelines, changes to medicines reimbursement and licensing, educational, professional body news and more. And finally, on the back cover you will find our COVID-19 resources for Oncologists, and a summary of upcoming local and international educational opportunities including workshops, webinars and conferences.

We hope you enjoy this Research Review publication and look forward to hearing your comments and feedback.

Kind Regards,

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Clinical Practice

NCCN Clinical Practice Guidelines in Oncology

2023 updates to the US National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for the management of mesothelioma - both pleural and peritoneal - have been published (version 1.2023 and version 2.2023, respectively). In recognition of the definition of all mesotheliomas as malignant the previous title of "Malignant Peritoneal Mesothelioma" has been changed to "Mesothelioma: Peritoneal", in-line with the title of the pleural mesothelioma guideline.

Developed by panel members, the key changes to the peritoneal document include modernisation of the pathology section to include unique molecular features that may aid in diagnosis of mesothelioma, differentiation from other carcinomas and between pleural and peritoneal mesothelioma types. Although determination of histologic subtype is complication by the inter- and intra-tumoral heterogeneity, prognostic variation with treatment ramifications make classification essential. Following obtainment of nodule/mass biopsy sample, histologic and immunohistochemistry (IHC) analysis is required to confirm a malignant pathologic diagnosis of diffuse disease and determine histologic subtype (epithelioid, sarcomatoid or biphasic, differentiated based on cytologic features). IHC with a panel of markers is required including both positive markers (mesothelial markers such as calretinin and podoplanin [D2-40]) and negative markers to exclude mimics (carcinoma markers such as claudin 4, thyroid transcription factor 1 [TTF-1], polyclonal carcinoembryonic antigen [CEA], and paired box gene 8 [PAX8]) plus others such as D2-40/podoplanin and GATA3. Other diagnostic methods including targeted next-generation sequencing, fluorescence in situ hybridisation and single-nucleotide polymorphism arrays are also available to identify cytogenetic and/or molecular features such as aberrant BRCA1-associated protein-1 (BAP1) protein expression and cyclin-dependent kinase inhibitor 2A deletions.

Pertinent updates in the 2023 version of the Mesothelioma: pleural guidelines include:

- use of BAP1 IHC as a surrogate diagnostic marker for *BAP1* genomic status (absence of BAP1 staining is found in ~50%–70% of mesothelioma epithelioid type and <20% of sarcomatoid type)
- in the molecular features section a bullet point was added to note the presence of distinct molecular features of peritoneal versus pleural mesothelioma and to emphasise that oncogenic *EWSR1-ATF1* fusion can be found in both

Iterations of guidelines on the diagnosis and treatment of malignant pleural mesothelioma from the American Society of Clinical Oncology, the British Thoracic Society and the European Respiratory Society/ European Society of Thoracic Surgeons/European Association for Cardio-Thoracic Surgery/European Society for Radiotherapy and Oncology - published in 2018, 2018 and 2020, respectively - have not been recently updated. The 2022 European Society for Medical Oncology (ESMO) updated their 2010 iteration in 2022. This is discussed in the **News in Brief** section of this document.

The complete and most recent versions of the NCCN guidelines are available free of charge at www.NCCN.org

European epidemiology of pleural mesothelioma—Real-life data from a joint analysis of the Mesoscape database of the European Thoracic Oncology platform and the European Society of Thoracic Surgery Mesothelioma database

In order to delineate the epidemiology and treatment outcomes for patients with pleural mesothelioma in Europe an analysis of two cohorts diagnosed between 1989 and 2019 was undertaken. Data on 2,766 patients derived from the European Thoracic Oncology Platform (n=497) – a mix of retrospectively and prospectively collected data from the Mesoscape translational research project – and the European Society of Thoracic Surgeons clinical database (n=2,269) were included in the analysis.

The study population was predominantly male (74%), exposed or possibly exposed to asbestos (85%) with a high prevalence of current or former smokers. The most common histologic subtype was epithelioid, accounting for almost three-quarters of cases, with biphasic and sarcomatoid histologies found in 18% and 8%, respectively. Disease was frequently not diagnosed until an advanced stage, with clinical staging estimating stage 3/4 disease in 57% of patients, a proportion that was upgraded to 69% after pathologic staging. Evaluation of biomarkers in patients with relevant data found that most patients were positive for calretinin, WT1, D2-40, CK 5/6 and Pan-CK, while Ber-EP4 and MOC-31 were detected only in 11%-14% of patients, and TTF-1 and CEA rarely. With regard to histologic subtype, patients with non-epithelioid mesothelioma were more likely to have been exposed to asbestos, tended to be older and male with higher stage disease and were biomarker positive less frequently versus patients with epithelioid histology (91% vs 99%; $p<0.001$), especially for WT1 and Ber-EP4. While there was no standardised treatment strategy across European countries, roughly 60% of patients received upfront multi-modal therapy macroscopic complete resection and 40% were treated palliatively. Kaplan-Meier curves with a median follow-up of almost four years found a median overall survival (OS) duration of 17.4 months (one- and two-year OS rates, 65% and 36%, respectively), although median OS was significantly different in the two individual cohorts (21.3 vs 14.8 months). Epithelioid histology, lower clinical stage and female sex were all identified as factors prognostic for favourable survival. More specifically, the significantly improved median OS in patients with epithelioid versus non-epithelioid histology subtypes (OS; 20.4 vs 11 months; one-year OS rate, 73% vs 46%) conferred a reduced risk of mortality on Cox proportional hazards modelling with a hazard ratio of 0.52. The inverse relationship between clinical stage and survival duration (median OS for clinical stage 1, 2, 3 and 4: 24.8, 19.1, 17 and 11.7 months, respectively) translated into increased mortality risks of 34%, 49% and over 200% with clinical stages 2, 3 and 4 versus 1, respectively. Finally, multimodal treatment compared to palliative intent therapy was associated with a significantly reduced mortality risk (hazard ratio, 0.56).

The study authors concluded their publication by emphasising the meagre improvements in diagnosis, staging and therapy for pleural mesothelioma over the 30-years up to 2019 and the critical importance of identifying novel therapeutic approaches to optimise the likelihood of survival.

J Thorac Oncol. 2023;18(9):1233-47

Mesothelioma in Australia 2021

In April this year the **Mesothelioma in Australia 2021** report was released by the Australian Institute of Health and Welfare. Utilising data from the Australian Mesothelioma Registry, the National Mortality Database and the Australian Cancer Database the estimated number of new diagnoses in 2021 was 722 (age range, 19-100; median age, 77 years). This figure is in keeping with the growing incidence across both genders over the last 40 years, with a 360% increase in cases from 1982 to 2021 (157 to 722), keeping Australia as the country with one of the worst rates in the world, along with Luxembourg, the UK, the Netherlands and New Zealand (Global incidence). Diagnoses in 2021 were predominantly in older males, most of which (90%) could be attributed to a possible or probable exposure to asbestos. Given the discrepancy between the extended latency period between asbestos exposure and mesothelioma development - estimated at up to 60 years - and the timeframe of asbestos ban (20 years ago), the high incidence may not come down for many years to come. Western Australia had the highest incidence of any state in 2021 (3.4 cases per 100,000 people), which can likely be credited to the history of asbestos mining in this state.

The 700 deaths in 2020 translated into a mortality rate of 2.1 deaths per 100,000 population. While still poor, temporal trends show modest improvements in survival, with a 10% increase in one-year relative survival between the periods 1989-1993 and 2014-2018, to a zenith of 47.1%. Marginal improvements in three- and five-year relative survival rates were also observed (13.6% vs 9.3% and 6.8% vs 5.6%, respectively).

Mesothelioma in Australia 2021– in focus

Results from NIPU trial of UV1 vaccine expected imminently

A news release from one of the sponsors of the multi-national, phase 2, proof of concept NIPU trial reports that the long-awaited top-line results will be presented in late October this year at the 2023 ESMO Congress.

The trial aimed to evaluate whether the efficacy of second-line doublet immunotherapy targeted to programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) in refractory malignant pleural mesothelioma can be augmented by concomitant vaccination with UV1 peptide vaccine to activate an immune response to the tumour-related antigen telomerase. Patients with unresectable pleural mesothelioma that progressed on first-line standard platinum doublet chemotherapy were accrued from Australia, Denmark, Norway, Spain and Sweden (n=118) from June 2020 and allocated to up to two years of nivolumab plus ipilimumab ± eight intradermal injections of UV1 vaccine. The primary efficacy outcome measure is progression-free survival (PFS) in the two trial arms per modified response evaluation criteria in solid tumours (RECIST) criteria by blinded, independent central review. Secondary efficacy measures include OS, objective response rate, disease control rate, time to response and duration of response. Exploratory objectives of the trial include evaluation of biomarkers of response to therapy, including tumour mutational burden and differences in tumour immune cell infiltration before and after therapy with and without the vaccine. As well as informing management of relapsed/refractory pleural mesothelioma it is hoped that results may also be indicative of the utility of incorporation of vaccination into front-line combination regimens.

As reported by Ultimovacs, a significant progression-free survival benefit to the addition of UV1 to the immunotherapy doublet was found by investigator assessment but not by blinded independent central review. Analysis of immature survival data indicated a potential survival advantage with UV1, with definitive conclusions not possible until data matures.

Positive preliminary efficacy for UV1 has been demonstrated in other telomerase-expressing tumours including prostate cancer and melanoma. In a phase 1 dose-escalation study in men with newly diagnosed metastatic hormone-naïve prostate cancer without visceral metastases most patients mounted an immune response to UV1 peptides following a 13-injection vaccine schedule on a background of androgen deprivation therapy and potential clinical benefit was reported (Cancer Immunol Immunother. 2017;66[7]:891-901). Encouraging preliminary efficacy for UV1 in combination with pembrolizumab was reported in a phase 1 trial in 30 treatment-naïve patients with advanced melanoma (Clin Cancer Res. 2023; 29[16]:3026–36).

Åslaug Helland, Professor at Oslo University Hospital, will present the results on Sat 21st October during the, 'Non-metastatic NSCLC and other thoracic malignancies' oral session (Abstract LBA99; title: First survival data from the NIPU trial; A randomized, open-label, phase II study evaluating nivolumab and ipilimumab combined with UV1 vaccination as second line treatment in patients with malignant mesothelioma; ESMO Congress 2023). The presentation can be viewed by registered conference attendees in person in Madrid, Spain or virtually through the online portal and will be published subsequently in a supplement to *Annals of Oncology*.

The press releases from Ultimovacs can be found here and here

MARS 2: A multicentre randomised trial comparing (extended) pleurectomy decortication versus no radical surgery for mesothelioma

The UK randomised MARS 2 (Mesothelioma and Radical Surgery 2) trial aimed to elucidate whether lung-sparing radical surgery with pleurectomy decortication improves survival in patients with resectable pleural mesothelioma when used in combination with platinum-based chemotherapy, given the demonstrated lack of survival benefit in this population with extra-pleural pneumonectomy and partial pleurectomy. A total of 335 patients at least 16 years of age with confirmed pleural mesothelioma of any histology confined to one hemi-thorax and deemed surgically resectable were accrued from National Health Service hospitals. Patients allocated to the control arm were administered the current standard of care with up to six cycles of platinum and pemetrexed chemotherapy (n=166). Patients randomised to the surgical arm underwent standard or extended parietal and visceral pleurectomy decortication surgery to remove all gross tumour ± diaphragm and/or pericardial resection. The surgical cohort also received six cycles of chemotherapy, with two cycles administered preoperatively and four in the adjuvant setting.

Results from MARS 2 were presented during plenary session 3 at the 2023 World Conference on Lung Cancer by Mr Eric Lim, a thoracic surgeon based at Royal Brompton Hospital in London. Analysis with a median follow-up of almost two years found an almost six-month longer median OS in the non-surgical versus the surgically treated cohort (24.8 vs 19.3 months) that translated into a 28% increased risk of mortality in the first 3.5 years after surgery (hazard ratio, 1.28), falling far short of the prespecified minimally important difference of 30% (hazard ratio 0.7) to demonstrate superior benefit with surgery over chemotherapy alone. No benefit to surgery was found in terms of delaying disease progression. The risks associated with pleurectomy decortication were substantial, with a 3.6-fold elevated risk of serious adverse events and significantly increased odds of symptoms including pain, dyspnoea and insomnia, amongst others, compared to chemotherapy alone. The authors concluded that given the multiple clinical trials failing to find any benefit to surgical intervention in mesothelioma deemed operable, it may be time for a paradigm shift to remove the concept of resectability and expand access to systemic therapies such as immunotherapy to this population in order to improve survival.

The conference abstract can be viewed here

Real world outcomes of immunotherapy for pleural mesothelioma in Australia - RIOMeso

At the recently held International Association for the Study of Lung Cancer 2023 World Conference on Lung Cancer, Dr Ned McNamee from the Kinghorn Cancer Centre in Sydney presented an analysis of outcomes in patients with unresectable pleural mesothelioma who received doublet immunotherapy in routine clinical practice in Australia. Retrospective analysis of the AURORA (AUstralian Registry and biObank of thoRacic cAncers) database identified 89 patients treated in any line setting with nivolumab plus ipilimumab. The cohort were predominantly older men (83% male; median age 73 years) with a confirmed asbestos exposure. With just over a one-year median follow-up, a median OS of 13.7 months was found, an outcome that wasn't significantly different between epithelioid versus non-epithelioid histologies (15.4 vs 13.0 months, respectively; p=0.63). One-quarter of patients experienced severe adverse events and two deaths were attributed to treatment. The most common serious adverse event was colitis (grade ≥2, 11%; grade ≥3, 8%). Twenty-eight percent of patients discontinued treatment due to toxicity.

The abstract from the conference can be found here

Determining the clinical utility of a breath test to screen asbestos-exposed persons for pleural mesothelioma

Non-invasive screening for pleural mesothelioma in individuals exposed to asbestos may be possible via a breath test to detect volatile organic compounds, according to results from the ongoing MESOBREATH 5 study presented by Kevin Lamote from the University of Antwerp in Belgium, at the International Association for the Study of Lung Cancer 2023 World Conference on Lung Cancer. The pilot study is evaluating the utility of multicapillary column/ion mobility spectrometry to detect latent disease in individuals with a history of substantial occupational asbestos exposure (at least 15 fibre years with first exposure at least 30 years ago). Over the four-year study period participants will undergo four breath tests, one at baseline and three annual follow-up tests plus correlative thoracic computed tomography scans. To date, 121 asbestos-exposed individuals and seven control patients with confirmed pleural mesothelioma have completed the first post-baseline breath test. Preliminary results, simultaneously published in the *Journal of Breath Research*, showed excellent sensitivity and negative predictive value of the test (both 100%), with all patients with mesothelioma testing positive and 55% of the test group testing negative. Accuracy, specificity and positive predictive value all seem low at the moment. The 45% of individuals with aberrant breath tests will undergo low-dose computed tomography imaging to confirm the presence/absence of a pleural tumour and correlate positive breath test results with radiological evidence.

The abstract from the conference can be found here

Clinical outcomes associated with pembrolizumab monotherapy among adults with diffuse malignant peritoneal mesothelioma

Single-agent pembrolizumab has anti-cancer activity in peritoneal mesothelioma, according to findings from a US retrospective dual-centre cohort study, suggesting its utility may be expanded beyond pleural mesothelioma. A total of 24 patients with diffuse malignant peritoneal mesothelioma who received single-agent pembrolizumab (median of seven 21-day cycles of 200 mg every 21 days) in the five-year period spanning 2015 to 2019, inclusively, through the University of Pennsylvania Hospital Abramson Cancer Centre or the Memorial Sloan Kettering Cancer Centre were included in the study and followed for up to seven years (median follow-up 29.2 months). Most patients had received prior systemic chemotherapy (median of two prior lines of therapy), two-thirds had undergone cytoreductive surgery and one-third had received prior intraperitoneal chemotherapy. The median patient age was 62 years and the predominant histology was epithelioid (75%). Analysis of efficacy in 19 evaluable patients with radiologic data revealed an objective response rate of 21.1%, comprised entirely of partial responses. Achievement of stable disease in 52.6% of patients resulted in a disease control rate of 73.7%. The median PFS and OS from pembrolizumab initiation were 4.9 and 20.9 months, respectively. A durable response with disease progression halted for at least two years was reported in three patients. Whilst favourable outcomes with numerically longer PFS and OS were found in patients with non-epithelioid versus epithelioid histology statistical significance was not reached. Further, responses showed no association with PD-L1 expression status (PFS in PD-L1-positive vs PD-L1 negative, 3.1 vs 5.7 months) or the presence of a *BAP1* alteration. The authors commented on the need to ascertain the predictive role of histology and biomarkers to immunotherapies in peritoneal mesothelioma.

JAMA Netw Open. 2023;6(3): e232526

News in Brief

Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

A new version of the ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of pleural mesothelioma, an update to the 2015 iteration, has been published. Recommendations are provided on surgical intervention as part of a multi-modal strategy for resectable disease with perioperative chemotherapy and a treatment algorithm details options, including immunotherapy, for patients deemed inoperable, as well as salvage therapies.

Ann Oncol. 2022;33(2):129-42

Germline variants incidentally detected via tumor-only genomic profiling of patients with mesothelioma

Universal germline screening may be warranted in patients with mesothelioma, with this case series of 161 patients with pleural or peritoneal mesothelioma finding that 16% of patients harboured a pathogenic germline variant that was incidentally detected on tumour-only sequencing (positive predictive value, 20%). Paired germline and tumour samples were analysed by next-generation sequencing, with results showing that germline pathogenic variants were most commonly found in genes involved in DNA repair, such as *BAP1*, *CHEK2* and *ATM*, although variants in at least 10 other genes were also found.

JAMA Netw Open. 2023;6(8): e2327351

Adjuvant dendritic cell-based immunotherapy after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with malignant peritoneal mesothelioma: a phase II clinical trial

Findings from the Dutch open-label MESOPEC trial suggest that adjuvant autologous dendritic cell-based immunotherapy (DCBI) is safe and feasible following cytoreductive surgery plus heated intraperitoneal chemotherapy (HIPEC) in patients with peritoneal mesothelioma. A total of 16 patients with disease confined to the abdominal cavity underwent leukapheresis prior to cytoreductive surgery to isolate monocytes from which to create the MesoPher dendritic cell vaccination. Briefly, monocytes were differentiated into dendritic cells and pulsed with allogeneic tumour associated antigens prior to injection back into the patient in three biweekly vaccinations plus boosters at three and six months. DCBI was reported to induce memory T-cell activation and had an immune modulatory effect on lymphoid cells. Outcomes included a median PFS of 12 months. Median OS was not reached.

J Immunother Cancer. 2023;11(8): e007070

Cytoreductive surgery and heated intraperitoneal chemotherapy for peritoneal mesothelioma: Canadian practices and outcomes

Deban et al retrospectively analysed the protocols for cytoreductive surgery and HIPEC utilised in Canada for peritoneal mesothelioma. In a cohort of 72 patients (mean age 52 years; 37.5% male), most underwent cytoreductive surgery plus HIPEC while one-third received neoadjuvant chemotherapy. The most commonly utilised HIPEC regimen was cisplatin plus doxorubicin and almost 70% of surgeries were via the semi-closed coliseum technique. A five-year OS rate of 61% and five-year recurrence-free survival rate of 35% were reported.

J Surg Oncol. 2023;128(4):595-603

COVID-19 Resources for Oncologists

Cancer Australia

The Royal Australian and New Zealand College of Radiologists

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European Society of Medical Oncology

American Society of Clinical Oncology

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Colorectal Oncology Research Review with Dr Matthew Burge and Dr Genni Newnham

Genitourinary Cancer Research Review with Associate Professor Andrew Weickhardt

Gynaecological Cancer Research Review with Drs Geraldine Goss and Inger Olesen

Lung Cancer Research Review with Dr Malinda Itchins and Dr Divyanshu 'Divy' Dua

Melanoma Research Review with Professors Michael Henderson and Peter Hersey

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